## II. REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

**Claim Status**

Claims 5-6, 9-10, 14-15, 18-19, and 22-27 were previously cancelled without prejudice or disclaimer.

Claims 8, 13, 17, and 21 are now cancelled without prejudice or disclaimer.

Claims 1-3, 7, 11, 16, and 20 currently are being amended. No new matter is added by the amendments. Support for the amendments can be found throughout the specification and claims as originally filed.

Support for the "range of 500 to 4900 $mg/m^2$" for DMXAA or the pharmaceutically acceptable salt thereof in claims 1 and 7, can be found, for example, in paragraph bridging pages 15-16 of the application as filed. Support for the potentiating ratio in claims 1, 7, 11, 16, and 20 and range of 1:100 to 1:2, in claim 2 can be found, for example, on page 4, lines 17-24 of the application as filed.

Claim 3 is amended for proper claim dependency.

Claim 28 is being newly added. No new matter is added by the new claim. Support for the new claim can be found, for example, in bridging paragraph between pages 22-23 of the application as filed.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-4, 7, 11-12, 16, 20, and 28 are now pending in this application. In view of the preceding amendments and the remarks that follow, reconsideration and withdrawal of the objections and rejections is respectfully requested.

**Information Disclosure Statement (IDS)**

Applicant thanks the Office for acknowledging the Information Disclosure Statement submitted on March 23, 2009.

**Claim Rejections under 35 U.S.C. § 112, Second Paragraph**

Claims 7-8 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office alleges that the limitation of "an effective amount" renders the claim indefinite because it is not clear for what the amounts are effective or what amounts are considered by the Applicant as effective amounts. See paragraph bridging pages 2-3 of Office Action dated May 1, 2009.

Without acquiescing to the propriety of the rejection and solely to expedite prosecution, Applicant has amended claim 7 to clarify that the claimed dosage is effective for treating a solid cancerous tumor in a mammal in need of such treatment.

Applicant also submit that the claim should be read in light of the specification which clearly identifies the effective amount. For example, pages 15-16 of Applicant's specification discloses suitable effective doses of DMXAA or the pharmaceutically acceptable salt thereof for the treatment of cancer. Page 17 discloses suitable effective doses of gemcitabine for the treatment of cancer. Page 15, lines 15-21 also discloses that the amounts of the agents will vary depending on the route of administration, nature of the formulation, mammal's body weight, age and general conditions, and the nature and severity of the disease to be treated, and that the amount is ultimately at the discretion of the medical practitioner. Therefore, Applicant's disclosure provides sufficient guidelines as to the effective amount based on the intended utility and how one skilled in the art can determine specific values for patient to be treated. Accordingly, in view of the preceding amendments and the remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

**Claim Rejections under 35 U.S.C. § 103**

1. Claims 1-4, 7-8, 11-13, 16-17 and 20-21 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Peters *et al.* (Pharmacology & Therapeutics, 2000, vol. 87, pages 227-253, "Peters" herein), Grindley *et al.* (US Patent No. 5,464,826, "Grindley" herein) and van Moorsel *et al.* (Biochemical Pharmacology, 1999, vol. 57, pages 407-415, "van Moorsel" herein) in view of Siemann *et al.* (Proceedings of the American Association for Cancer Research, 2000, vol. 41, page 525, "Siemann" herein) and Pruijn *et al.* (Cancer Chemother. Pharmacol., 1997, col. 39, pages 541-546, "Pruijn" herein). Further to the last Office Action, the Office has now cited Peters in this Office Action alleging that Peters teach that antimetabolites are widely used in combination therapy and that a promising new type of combination is antimetabolite with inhibitor of angiogenesis. The Office further points to Table 1 and 5 of Peters which allegedly discloses combination of gemcitabine with other anticancer agents. See page 4 of the Office Action.

Without acquiescing to the propriety of the rejection and solely to expedite prosecution, Applicant has amended claims to focus the claim scope to potentiating ratio of DMXAA or the pharmaceutically acceptable salt thereof and gemcitabine. Claim 1 also defines an amount of DMXAA or the pharmaceutically acceptable salt thereof comprising a range of 500 to 4900 $mg/m^2$. Claim 2 now defines the potentiating ratio to be in a range of 1:100 to 1:2.

None of the cited references, namely, Peters, Grindley, van Moorsel, Siemann and Pruijn, individually or in combination teach or suggest any potentiating ratio of DMXAA or the pharmaceutically acceptable salt thereof and gemcitabine or an amount of DMXAA or the pharmaceutically acceptable salt thereof comprising a range of 500 to 4900 $mg/m^2$ or the potentiating ratio to be in a range of 1:100 to 1:2. Therefore, neither of the cited references teach or suggest all the claim limitations of instant amended claims. For this reason alone, this rejection under 35 U.S.C. § 103(a) is now moot.

Nevertheless, Applicant rebuts the arguments presented by the Office in the Office Action as follows.

The U.S. Supreme Court, in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007), noted that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." The Court held that the teaching, suggestion, motivation "TSM" test must be applied flexibly, and take into account a number of factors "in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1740-41. Despite this flexibility, however, the Court stated that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does." *Id.* "To facilitate review, this analysis should be made explicit." *Id.*

The Office has relied on Siemann and Pruijn for the motivation to combine the teachings of the primary references. Presently, the Office has added the teachings of Peters for combining the disparate teachings of the prior art. In view of the following remarks, Applicant submits that the Examiner has not articulated a reason as to why a skilled artisan, in considering the teachings of all the references as a whole, would be motivated to combine DMXAA with gemcitabine to treat solid tumors.

Peters advocates the use of rationally designed preclinical evaluations as a basis for combining therapy. Peters teaches that whenever a new combination is contemplated, it is necessary to consider the biochemical mechanism that serves as a basis for the action and the interaction of the agents (see page 228, right hand column). Peters discloses that mechanistic studies show that gemcitabine affects DNA repair and that based on the mechanism of gemcitabine, it can be combined with other agents that cause direct DNA damage or form DNA adducts (see page 245, left hand column). Therefore, Peters teaches combination of gemcitabine with agents that are an inhibitor of angiogenesis or with an agent that specifically either causes DNA damage or forms DNA adducts. Examples of such agents in Peters include, cisplatin, 5-fluouracil (5-FU), mitomycin, docetaxel and paclitaxel, ifosfamide, navelbine, etoposide, doxorubicin, and epirubicin.

As the Office noted, Peters on page 233, advocates the combination of an antimetabolite with inhibitors of angiogenesis. Applicant submits that Peters does not provide the motivation to combine since DMXAA is not an angiogenesis inhibitor. DMXAA is a low molecular weight tumor-vascular disrupting agent which targets established blood vessels, resulting in tumor ischemia and necrosis. An angiogenesis inhibitor, in contrast, interferes with a new blood vessel formation and therefore have a preventative action. See Siemann et al. *Clinical Cancer Research* 11:416-420 (2005), **Exhibit I**.

Finally, Peters, does not teach, suggest or motivate using a potentiating ratio of gemcitabine with another anticancer agent, let alone DMXAA, an express element of all pending claims.

Therefore, in the absence of any reason to combine gemcitabine of Peters with a tumor-vascular disrupting agent, such as DMXAA, a skilled artisan will not be motivated to pick different chemotherapeutic agents from disparate art cited by the Office to arrive at the combination of the claimed invention.

In fact, the Office has resorted to impermissible hindsight by picking and choosing different chemotherapeutic agents from disparate teachings of the art. The predecessor court to the Federal Circuit, the United States Court of Customs and Patent Appeals, cautioned examiners against the use of hindsight in obviousness determinations. In reversing a finding of obviousness of an invention to a ball point pen, the Court of Customs and Patent Appeals in *In re* Shuman, 361 F.2d 1008, 1012 (C.C.P.A. 1966) noted that, "[r]eferences are evaluated by ascertaining the *facts fairly disclosed therein as a whole*. It is impermissible to first ascertain factually what appellants *did* and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants' invention from such prior art." *Id.*

Twenty years later the Federal Circuit echoed the *Shuman* admonition in vacating a summary judgment based on § 103 obviousness. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132 (Fed. Cir. 1985). Holding that the inventor's telephone switching system was not obvious,

the Federal Circuit stated that to determine compliance with § 103 the "invention must be viewed not with the blue-print drawn by the inventor, but in the state of the art that existed at the time." *Id.* at 1138. Because what might seem clear and obvious in light of a fully diagrammed invention "may have been a breakthrough of substantial dimension," obviousness must be determined based on the skill and art at the time of the invention without applying a filter based on the inventor's design. *Id.*

Consistent with the above rulings, Applicant submits that the Office has engaged in impermissible hindsight and has used the claimed invention as a road map to select only those portions from the art and modified them to reconstruct Applicant's invention.

The Office has cited Grindley to show that gemcitabine is known to be a compound effective in treating cancer such as solid tumors. Applicant submits that while Grindley may teach such, it does not fulfill the deficiency of the suggestion or motivation in Peters to combine gemcitabine with DMXAA.

The Office has cited van Moorsel that discloses a combination of gemcitabine with etoposide, a topoisomerase II inhibitor. The Office alleges that the reference motivates combining gemcitabine with other anticancer agents in the treatment of cancer. Similar to Peters, van Moorsel also fails to suggest or motivate a skilled artisan to use gemcitabine with a tumor-vascular disrupting agent, such as DMXAA.

The Office cited Siemann for disclosing the use of a combination of DMXAA with cisplatin and cyclophosphamide. Applicant submits that the teachings of Siemann are limited. Firstly, Siemann does not teach or suggest an amount of DMXAA in a range of 500 to 4900 $mg/m^2$. Secondly, Siemann does not teach any potentiating ratio of DMXAA with the other anticancer agent. Finally, Siemann provides no suggestion or motivation to use DMXAA with gemcitabine and based on the teachings of Peters, the art as a whole teaches away from the combination of gemcitabine and DMXAA.

Moving on to Prujin, Applicant submits that Pruijn teaches combination of melphalan with DMXAA. The Office points to Pruijn that concludes that DMXAA induces

microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions. See Pruijn, page 545, right hand column, last line of last paragraph.

Applicant respectfully traverses. Gemcitabine is neither a bioreductive drug nor is it selective for cells under hypoxic or acidic conditions. Applicant had submitted Yokoi et al.[1] to show that hypoxia increases resistance of human pancreatic cancer cells to apoptosis induced by gemcitabine. Therefore, the hypoxic conditions induced by DMXAA, as taught in Pruijn et al., would increase the resistance of the cancer cells to gemcitabine, as taught in Yokoi et al. The Office alleges that Yokoi demonstrated only *in vitro* assays and that the fact that gemcitabine is not effective *in vitro* does not teach away from using gemcitabine in combination with DMXAA to treat solid cancerous tumor. See bridging paragraph of pages 9-10 of the Office Action dated May 1, 2009.

Applicant submits Huxham et al., "Microregional effects of gemcitabine in HCT-116 xenografts," *Cancer Res.* 64:6537-6541 (2004) (attached as **Exhibit II**) where an activity of gemcitabine against hypoxic cells in an *in vivo* model has been assessed. Huxham et al. demonstrate that cells distant from blood vessels in hypoxic regions of HCT-116 xenografts are resistant to gemcitabine (resume proliferation earlier after treatment than cells near blood vessels). The mechanism of this resistance is suggested to be due to limited penetration of gemcitabine through tumour tissue. See abstract of Huxham et al. On this basis, a skilled artisan would expect that interference with vascular perfusion and induction of hypoxia would decrease sensitivity to gemcitabine.

With reference to the demonstration made in Pruijn that DMXAA causes entrapment of melphalan in tumors caused by falling tumor blood flow, the Office is incorrect in stating that, "[o]ne skilled in the art would have been imbued with at least a reasonable expectation that DMXAA would have this effect on any known anticancer agent, including the instantly claimed gemcitabine." See page 6 of the Office Action dated May 1, 2009 (emphasis in original). Such

[1] In Response dated March 23, 2009

an effect would only be expected in the case of agents for which delivery to tumors is flow-limited and entrapment of the agent by inhibition of blood flow would require that its clearance from the tumor is due to blood flow (not, for example, metabolism in the tumor). See, for example, abstract and page 542 of Pruijn.

Therefore, in the absence of any teaching, suggestion or motivation in the cited references, either alone or in combination, there is no reason for a skilled artisan to use a combination of DMXAA with gemcitabine as in the claimed invention.

Further, Applicant demonstrated unexpected results in the specification and the Declaration by Hakim Djeha, in the Response filed March 23, 2009. The Office alleges that in the absence of statistical analysis of this data, one cannot say whether the difference between the data sets is statistically significant. See page 10 of Office Action dated May 1, 2009.

Applicant submits the statistical analysis in the Declaration by Hakim Djeha (attached as **Exhibit III**). The statistical analysis of this data establishes that the difference in relative tumor volumes of the treatment groups are statistically significant and not merely additive.

Thus, Applicant herein provides evidence contradictory to the *prima facie* evidence of record and supplementary evidence of unexpected results of the claimed invention. Accordingly, the prior art as a whole does not teach or suggest the claimed invention and the rejection under 35 U.S.C. § 103 should be withdrawn.

The Office has again cited *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) and *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983) in support of its position in rejecting the claims under 35 U.S.C. §103(a). In the last Office Action dated December 22, 2008, the Office alleged that the Applicant had presented no evidence to rebut the natural presumption that two agents which are known to be effective to treat cancer as individual agents would also be effective when administered in combination.

In the Response dated March 23, 2009, Applicant provided ample evidence that corroborated Applicant's assertion that two anticancer agents are not expected to be effective in combination therapy by virtue of them being anticancer agents individually. Seeing the

unpredictability in the field of cancer treatment with combination therapy, a skilled artisan will have no reasonable expectation of success to combine two anticancer agents, namely, DMXAA and gemcitabine, in the manner claimed in the instant invention.

None of the references cited by the Office suggest (expressly or by implication) the combination of gemcitabine with DMXAA. There is no suggestion or motivation to combine the references and arrive at the synergistic combination of DMXAA and gemcitabine of the claimed invention.

Applicant has provided references, in the Response dated March 23, 2009, to show that it is not expected of the anti-cancer agents to be effective in combination therapy by virtue of them being anticancer agents individually. Yokoi K. et al. and Huxham et al. show that gemcitabine is not effective under hypoxic conditions induced by DMXAA. Therefore, a skilled artisan will have no reasonable expectation of success in combining gemcitabine with DMXAA in the manner claimed in the invention. Finally, the statistical analysis provided in the Declaration supports the surprising and unexpected results in using the combination therapy of the claimed invention.

In light of the above, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a).

2. Claims 1-4, 7-8, 11-13, 16-17 and 20-21 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Davis et al. (WO 00/48591, "Davis" herein) in view of Peters et al. (Pharmacology & Therapeutics, 2000, vol. 87, pages 227-253).

Applicant traverses for the following reasons:

Davis discloses that the efficacy of vascular damaging agents can be improved by combining the treatment with inhibitors of the formation or action of nitric oxide (see Davis, page 2, lines 7-9). Davis teaches a laundry list of anticancer agents that may be used in combination with DMXAA and NO synthase inhibitor, such as, mitotic inhibitors; alkylating agents; antimetabolites; intercalating agents; enzymes; topoisomerase inhibitors; thymidylate synthase inhibitors; biological response modifiers; antibodies; and anti hormones which are

further defined by various species. Therefore, Davis discloses a general class of antimetabolites in this laundry list. Davis does not disclose any potentiation of the vascular damaging agents and the inhibitors of nitric oxide with any other additional agent and more specifically, gemcitabine, let alone a potentiating ratio of DMXAA with gemcitabine.

There is no suggestion or motivation to modify Davis to arrive at the claimed invention because such modification would require: 1) the selection of the additional therapy (i.e., an antimetabolite, such as gemcitabine) for substitution amongst a laundry list of possibilities; and 2) the selection of the potentiating ratio for composition.

The Courts have reviewed the issue of the specific versus general teachings present in the prior art and the applicability in supporting a *prima facie* case of obviousness.

The Federal Circuit ruled that the prior art did not render obvious the claimed invention because, "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007), *cert. denied*, 128 S.Ct. 1739 (2008).

This application of the law was affirmed by the Federal Circuit in *Eisai Co. Ltd., v. Dr. Reddy's Lab., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008), *reh'g denied, reh'g en banc, denied*, 2008 U.S. App. LEXIS 25264, (Fed. Cir., Sept. 16, 2008), wherein the Federal Circuit stated: "[t]hird, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions ..."

In *Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc.*, 545 F.3d 1312 (Fed. Cir. 2008), the Federal Circuit ruled that the U.S. Patent No. 5,236,940 (the "'940 patent") of the Plaintiff, Impax Laboratories Inc., was not enabled and thus the U.S. Patent No. 5,527,814 (the "'814 patent") of the defendant, Aventis Pharmaceuticals Inc., was not anticipated. The Court agreed with the district court finding that the '940 patent embraces in formula I hundreds or thousands of compounds and several diseases and that nothing in the '940 patent would direct

one skilled in the art to recognize that riluzole could be used to treat ALS. The Court further agreed with the district court rejection of the notion that mere mention of riluzole is sufficient to put one skilled in the art in the possession of the claimed invention. *Id.* at 6. The Court ruled that the trial court's findings properly support its conclusion that an ordinary skilled artisan would have needed to experiment unduly to gain possession of the claimed invention. *Id.* at 7.

Analogous to above rulings, Davis does not suggest or direct a person of ordinary skill in the art to pick and choose an antimetabolite, such as gemcitabine, amongst this list of anticancer agents to arrive at the claimed invention. Further, Davis does not teach any potentiation effect between DMXAA and gemcitabine. Mere mention of antimetabolite is not sufficient to motivate one skilled in the art to pick gemcitabine to arrive at the claimed invention.

Meanwhile, Peters shows combination of gemcitabine with agents that have the similar mechanism of action as gemcitabine. As explained supra, Peters does not suggest or motivate a skilled artisan to choose DMXAA which has an entirely different mechanism of action than gemcitabine and use it in combination with DMXAA.

With respect to reasonable expectation of success, Applicant submits that due to absence of any suggestion or motivation in Davis to pick and choose gemcitabine from a long list of anticancer agents and due to unpredictability in the field of cancer therapy, a skilled artisan would have no reasonable expectation of success to arrive at the claimed invention.

In light of the above, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

## III. CONCLUSION

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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